I. BORON TRIFLUORIDE AS A CONDENSING AGENT IN THE FISCHER INDOLE SYNTHESIS

II. CARBON-ALKYLATION WITH QUATERNARY AMMONIUM SALTS. A NEW SYNTHESIS OF TRYPTOPHAN AND OTHER COMPOUNDS CONTAINING THE 3-INDOLEMETHYLENE GROUP

BY

CURTIS WILLIAM SMITH

B. Ed., Southern Illinois State Normal University, 1940

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE SCHOOL OF THE UNIVERSITY OF ILLINOIS, 1943

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PART I. BORON TRIFLUORIDE AS A CONDENSING AGENT IN THE FISCHER INDOLE SYNTHESIS

INTRODUCTION

Phenylhydrazones of carbonyl compounds containing a methylene group adjacent to the carbonyl group may be converted to the corresponding indoles with the loss of one molecule of ammonia. Most of the condensing agents which have been used to effect the conversion are acidic substances, ranging from mineral acids to metal halides. In many other reactions boron fluoride can be used in place of such condensing agents, often to advantage. The present work was undertaken to evaluate boron fluoride as a condensing agent for the indole synthesis.

DISCUSSION

Boron trifluoride has been found to be an excellent condensing agent in the Fischer indole synthesis, and its behavior under varied conditions has been investigated. Those phenylhydrazones which have been converted to indoles by the aid of other reagents generally have undergone the reaction under the influence of the new condensing agent. The boron fluoride may be used in various ways. The gas may be bubbled into a solution of the phenylhydrazone in an organic solvent, with subsequent heating of the mixture to bring about decomposition of the phenylhydrazone boron fluoride compound; if a non-polar solvent is used, this compound may separate as a heavy oil and the decomposition then may be effected by heating the oil either alone or under the solvent. Another technique consists in bubbling boron fluoride through a refluxing solution of the phenylhydrazone in a solvent such as benzene or xylene. Boron fluoride etherate may be employed to advantage, since the liquid etherate can be handled more conveniently than the gaseous boron fluoride.

An explanation has been offered for the intermediate coloration noted during the formation of indoles from phenyl-

hydrazones carrying no substituent on the α-nitrogen atom. This color phenomenon has been attributed to an equilibrium between the colorless phenylhydrazone and the colored phenylazo tautomer. The isomerization of phenylhydrazones, occasionally observed in unsuccessful or partly successful indole syntheses, also may be accounted for on the basis of this tautomerism.

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PART II: CARBON-ALKYLATION WITH QUATERNARY AMMONIUM SALTS. A NEW SYNTHESIS OF TRYPTOPHAN AND OTHER COMPOUNDS CONTAINING THE 3-INDOLEMETHYLENE GROUP.

INTRODUCTION

Although simple quaternary ammonium salts have been used as alkylating agents in the preparation of numerous sulfur [1], oxygen [2,3,4,5], and nitrogen [6,7] alkylated substances, they have not appeared promising as reagents for the preparation of carbon-alkyl derivatives. The present work was undertaken to discover whether such reactions can be effected.

DISCUSSION

Quaternary ammonium salts containing a radical of the benzyl type have been used in the alkylation of active methylene compounds. The active methylene compounds were employed as the sodium derivatives, and the products of the reaction were sodium halide, a tertiary amine and the C-benzyl (or aralkyl) active methylene compound. Certain side reactions have been observed. For example, from benzyldimethylphenylammonium chloride and the sodium derivative of ethyl malonate reacting in ethanol, only a five per cent yield of ethyl benzylmalonate was obtained, the major products being ethyl dibenzylmalonate and benzyl ethyl ether. When

the reaction was carried out in the absence of alcohols and with no solvent other than excess malonic ester, the yield of ethyl benzylmalonate was 80%. Under the same conditions benzyltriethylammonium iodide gave a yield of only 62.5%. Such salts may undergo decomposition to olefins, a side reaction which cannot occur with benzyldimethylphenylammonium chloride, and this may account for the lower yields.

This method of carbon-alkylation has been applied to the synthesis of a number of substances containing the 3-indolemethylene group; the methiodide of gramine (3-dimethylaminomethylindole) was used to alkylate malonic ester, acetoacetic ester, and cyanoacetic ester. 3-Indoleacetic acid was prepared by hydrolysis of the nitrile obtained from gramine methiodide and potassium silver cyanide.

A convenient and economical synthesis of *dl*-tryptophan has been accomplished using this type of carbon-alkylation. The methiodide of gramine was condensed with the sodium derivative of ethyl acetaminomalonate to give ethyl α-acetamino-α-carbethoxy-β-(3-indole)-propionate. The two ester groups were saponified and the resulting acid was decarboxylated in boiling water to give *dl*-N-acetyltryptophan Alkaline hydrolysis gave *dl*-tryptophan in an overall yield from indole of 50%. *dl*-Tryptophan was obtained in a similar manner from phthalimidomalonic ester but the yields were poorer and the reaction conditions were more drastic.

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VITA

The author was born in Omaha, Illinois, January 14, 1918. He was graduated from high school in Salem, Illinois, in 1935. He entered Southern Illinois State Normal University the next year and was granted the Bachelor of Education degree in June, 1940. In the fall of that year he began work in the Graduate School of the University of Illinois. From September, 1940, to February, 1941, he held a teaching assistantship, and from February, 1941, to June, 1942, he held a Special Research Assistantship. For the summer months of 1942 and 1943 he was a National Defense Research Assistant. He held a University Fellowship from September, 1942, to June, 1943.

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